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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,640	12/15/2003	Bruno de Lignieres	029488-0111	9061

22428 7590 12/16/2008

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EXAMINER	
RAMACHANDRAN, UMAMAHESWARI	
ART UNIT	PAPER NUMBER
1617	
MAIL DATE	DELIVERY MODE
12/16/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,640	LIGNIERES ET AL.	
	Examiner	Art Unit	
	UMAMAHESWARI RAMACHANDRAN	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/29/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/25/2008 has been entered.

Claims 1-14 are currently pending and are being examined on the merits herein.

Response to Remarks/Arguments

Applicants' arguments regarding the rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10, 11-14 under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congress International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claims 1-3, 6-8, 10,11-14 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) and rejection of claim 9 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498,

1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958) and rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988) have been fully considered but are moot in view of the new grounds of rejection. Further search and consideration necessitated the new rejections presented in this office action. Accordingly, the action is made non-final.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al. (Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teaches a method of treating conditions of the breast including the steps of: forming an aqueous alcoholic gel in which the active ingredient consists of 4-OH tamoxifen and administering percutaneously said aqueous alcoholic gel as an anti-estrogen drug to a breast (col. 4, claim 1). Jarvis et al. teaches that the daily doses of product to be administered are easy to calculate in terms of the absorption coefficients of the drugs and the doses which it is desired to obtain for 4-hydroxytamoxifen at the level of the receptor molecule (col.3, lines 23-28). The reference teaches that the drug 4-OH tamoxifen finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast (col. 4, lines 37-39).

Jarvis (Current Therapy in Endocrinology and Metabolism) studies teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease (p 281, col. 1, col. 2, Antiestrogens).

The references do not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12). The reference further teaches the agent proved to be significantly more effective in the relief of cyclical rather than non cyclical pain (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is

already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia in expectation of success because of the teachings of Jarvis and Fentiman. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease conditions (mastalgia, which includes both cyclical and non-cyclical is one of the symptoms of benign breast disease) and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. Mastalgia is breast pain and is generally classified as either cyclical (associated with menstrual periods) or noncyclic. Jarvis in essence teaches the use of 4-OH tamoxifen in the treatment of breast conditions including benign breast disease and breast pain being one of the symptoms of the breast disease is obviously treated upon administration of 4-OH tamoxifen.

Claims 1-3, 6-8, 10, 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in

view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988).

Jarvis et al. teaches a method of treating conditions of the breast including the steps of: forming an aqueous alcoholic gel in which the active ingredient consists of 4-OH tamoxifen and administering percutaneously said aqueous alcoholic gel as an anti-estrogen drug to a breast (col. 4, claim 1). Jarvis et al. teaches that the daily doses of product to be administered are easy to calculate in terms of the absorption coefficients of the drugs and the doses which it is desired to obtain for 4-hydroxytamoxifen at the level of the receptor molecule (col.3, lines 23-28). The reference teaches that the drug 4-OH tamoxifen finds application in the treatment of conditions of the breast, especially benign and even cancerous conditions of the breast (col. 4, lines 37-39).

Jarvis et al. (("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986) studies teaches breast pain (mastodynia or mastalgia) as one of the symptoms of benign breast disease and further teach that studies have been performed to determine if 4-hydroxy tamoxifen, a very active metabolite of tamoxifen that has an affinity for the estrogen receptor 100 times greater than that of tamoxifen, can be used percutaneously to avoid the systemic effects of the oral administration of tamoxifen in benign breast disease (p 129, 130, Therapeutic Alternatives, Antiestrogens).

The references do not teach the amount of 4-hydroxy tamoxifen in the percutaneous administration.

Pujol et al. teaches a percutaneous administration of 0.5 mg, 1.0 mg, 2.0 mg of 4-hydroxy tamoxifen in a hydroalcoholic gel to breast areas for the treatment of breast cancer (see Abstract, p 494, study design).

Jarvis and Pujol et al. do not teach mastalgia to be cyclical.

Fentiman teaches a method of treatment of mastalgia comprising oral administration of 10 or 20 mg of tamoxifen to patients with either cyclical or non-cyclical breast pain (see Abstract, p 845, col. 2, lines 10-12). The reference further teaches the agent proved to be significantly more effective in the relief of cyclical rather than non cyclical pain (see abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer 4-hydroxy tamoxifen at a dose of at least 1.5 mg/day or the dosages claimed in the instant invention. One of ordinary skill in the art would have been motivated to administer such claimed amounts of 4-hydroxy tamoxifen in the treatment of mastalgia because of expectation of success as Pujol et al. clearly teaches percutaneous administration of 4-OH-tamoxifen (0.5 mg and 1.0 mg/breast) to patients. The examiner respectfully points out the following from MPEP 2144.05: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." I*n re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages."); *In re Hoeschele*,

406 F.2d 1403, 160 USPQ 809 (CCPA 1969); Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed.Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). It would have been obvious to one of ordinary skill in the art to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia. One of ordinary skill in the art would have been motivated to use 4-hydroxy tamoxifen in a method of treatment of cyclical mastalgia in expectation of success because of the teachings of Jarvis and Fentiman. Jarvis teach the use of 4-hydroxy tamoxifen in benign breast disease conditions (mastalgia, which includes both cyclical and non-cyclical is one of the symptoms of benign breast disease) and Fentiman teaches the use of tamoxifen in the treatment of both cyclical and non-cyclical breast pain. Mastalgia is breast pain and is generally classified as either cyclical (associated with menstrual periods) or noncyclic. Jarvis in essence teaches the use of 4-OH tamoxifen in the treatment of breast conditions including benign breast disease and breast pain being one of the symptoms of the breast disease is obviously treated upon administration of 4-OH tamoxifen.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Jarvis ('937 patent), Jarvis (Curr Therapy Endocrin and Met), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

The prior art from Jarvis (both references), Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Kochinke et al. (U.S. 5,613,958).

The teachings of Jarvis ('937 patent), Jarvis ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

The prior art from Jarvis (both references), Pujol et al. and Fentiman et al. do not teach the hydroalcoholic gel comprising ethanol, isopropyl myristate and hydroxypropyl cellulose.

Kochinke et al. teaches a transdermal drug delivery system comprising a drug, plasticizer-type enhancer such as isopropyl myristate, a solvent-type enhancer such as ethanol and a gelling agent such as hydroxypropyl cellulose (col. 9, lines 23-25, 47-59, col. 11, lines 6-25).

It would have been obvious to one of ordinary skill in the art to use a combination of isopropyl myristate, ethanol, and hydroxypropyl cellulose as a hydroalcoholic gel solution in the percutaneous delivery of 4-OH tamoxifen. The motivation to do so is

provided by Kochinke et al. The reference teaches that solvent-type enhancer such as ethanol provide higher flux rate, plasticizer-type enhancer such as isopropyl myristate is used in combination with a solvent-type enhancer to deliver drugs through stratum corneum at therapeutically effective levels and to eliminate the irritation that occurs when solvent-type enhancers are used alone at high concentrations. In addition the reference teaches that a gelling agent such as hydroxypropylcellulose is added to increase the viscosity and rheological characteristics of the drug and enhancers.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis (Current Therapy in Endocrinology and Metabolism, 280-284) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Jarvis ('937 patent), Jarvis (Current Therapy in Endocrinology and Metabolism), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Jarvis ('937 patent) teaches the use of mixture of cis and trans isomers of 4-OH tamoxifen in a method of treating benign breast conditions. The reference further teach the separation of the isomers. However, the references discussed above do not explicitly teach the use of trans isomer alone in a method of treating a breast condition such as mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen and further teaches that cis isomer has estrogenic agonistic effect (p 7193, col.2, para 4, lines 11-12) and the antiproliferative effects are weaker than that of the trans isomer (p 7199, col. 1, lines 4-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a trans isomer of 4-OH tamoxifen in the treatment of mastalgia because of the teachings of Malet et al. Malet et al. reference teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen. The reference further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level. One having ordinary skill in the art would have been motivated to administer the trans isomer of 4-OH tamoxifen in the treatment of mastalgia because cis isomer has antiproliferative effects that are weaker than that of the trans isomer and cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect.

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jarvis et al .(Applicant cited IDS: U.S. 4,919,937) and Jarvis et al. ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris 1-4 September 1986, pp. 128-132) in view of Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and further in view of in view of Fentiman et

al. (Br. J. Surg, 75, 845-846, 1988) as applied to claims 1-3, 6-8, 10, 11-14 above and further in view of Malet et al (Cancer Research, 48, 7193-7199, 1988).

The teachings of Jarvis ('937 patent), Jarvis ("Hormonal Therapy of Benign Breast Disease," Senologie et Pathologie Mammaire.4eme Congres International, Paris), Pujol et al. (Cancer Chemother Pharmacol, 36, 493-498, 1995) and Fentiman et al. (Br. J. Surg, 75, 845-846, 1988) have been discussed in the 103(a) rejection set forth above.

Jarvis ('937 patent) teaches the use of mixture of cis and trans isomers of 4-OH tamoxifen in a method of treating benign breast conditions. The reference further teach the separation of the isomers. However, the references discussed above do not explicitly teach the use of trans isomer alone in a method of treating a breast condition such as mastalgia.

Malet teaches percutaneous administration of trans 4-hydroxy tamoxifen to human breast of patients (see Abstract). The reference further teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen and further teaches that cis isomer has estrogenic agonistic effect (p 7193, col.2, para 4, lines 11-12) and the antiproliferative effects are weaker than that of the trans isomer (p 7199, col. 1, lines 4-5).

It would have been obvious to one of ordinary skill in the art at the time of the invention to have administered a trans isomer of 4-OH tamoxifen in the treatment of mastalgia because of the teachings of Malet et al. Malet et al. reference teaches that trans-4-hydroxy tamoxifen is a very active metabolite of tamoxifen. The reference

further teaches that cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect and a percutaneous administration of trans 4-hydroxy tamoxifen could produce a strong antiestrogenic effect at the molecular level. One having ordinary skill in the art would have been motivated to administer the trans isomer of 4-OH tamoxifen in the treatment of mastalgia because cis isomer has antiproliferative effects that are weaker than that of the trans isomer and cis-4-hydroxy tamoxifen exerts a potent estrogenic agonistic effect.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to UMAMAHESWARI RAMACHANDRAN whose telephone number is (571)272-9926. The examiner can normally be reached on M-F 8:30 AM - 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SREENI PADMANABHAN/
Supervisory Patent Examiner, Art Unit 1617